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EXAMINER

KRASS, FREDERICK F

ART UNIT	PAPER NUMBER
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1614

DATE MAILED: 08/18/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/975,776

Applicant(s)

JIANG ET AL.

Examiner

Frederick Krass

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25, 28-80, 83-122 and 125-203 is/are pending in the application.

4a) Of the above claim(s) 7, 8, 10, 41, 42, 44, 52-80, 83-122, 125-179 and 188-203 is/are withdrawn from consideration.

- 5) ☐ Claim(s) _____ is/are allowed.

- 6) ☒ Claim(s) 1-4, 9, 11-25, 28, 30-38, 43, 45-49, 180, 181 and 183-187 is/are rejected.

- 7) ☒ Claim(s) 5, 6, 39, 40, 50, 51 and 182 is/are objected to.

- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.

- 10) ☒ The drawing(s) filed on 10 October 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8, 13, 14.

4) ☐ Interview Summary (PTO-413) Paper No(s). _____

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other:

Restriction Requirement

Applicant's election with traverse of Group I in Paper No. 12 is acknowledged. The traversal is on the ground(s) that claims 31-44 and 145-152 were misgrouped. The examiner agrees. Claims 31-44 and 145-152 are hereinafter to be considered part of elected Group I. Applicant does not appear to have otherwise traversed the restriction requirement.

Election of Species Requirement

Applicant's election of 1) an aqueous solution and 2) cyclodextrin as ultimate species in Paper no. 12 is acknowledged. Applicant has traversed the requirement, stating that the Markush group of solubilizers recited in instant dependent claims 4, 13, 23, 38, etc. is sufficiently few in number to justify simultaneous search. The examiner agrees. Furthermore, in accordance with Applicant's request, the election of species requirement should hereinafter be considered to be modified as an election between 1) aqueous solutions 2) oil solutions and 3) emulsions. Examination has been conducted based on Applicant's election of an aqueous solution.

Scope of Enablement Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9, 11, 12, 18, 19, 21, 22, 28, 30-37, 43, 45-48, 180, 181 and 183-187 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising B-lapachones and certain particular solubilizing agents, e.g. see instant claim 4, does not reasonably provide enablement for combinations of B-lapachones and other solubilizing agents generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1. The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art

While the relative skill of those in the art is high, this is outweighed by the highly unpredictable nature of the invention. The prior art recognizes that a long-standing problem exists with regard to solubilizing B-lapachone: see for example WO 00/61142 at page 21, lines 9 and 10. Thus, the ability of any given solvent to solubilize any given B-lapachone cannot be predicted *a priori*, and must be determined empirically on a case-by-case basis.

2. The breadth of the claims

The rejected claims are extremely broad and inclusive of any and all possible solubilizing agents.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no guidance for selecting any particular solubilizing agents, other than those specified in the working examples and recited in certain dependent claims (e.g. claim 4). In fact, the specification actually directs one away from using other solvents: see page 8, lines 5-8, for example.

4. The quantity of experimentation necessary

Applicant fails to provide information allowing the skilled artisan to ascertain which combinations of B-lapachones and solubilizing agents can reasonably be expected to produce compositions in which the B-lapachone is solubilized, let alone in which extremely high solubility is achieved (see instant claim 9, for example) or in which highly desirable characteristics of reconstitutability are obtained (see instant claims 11 and 21, for example). In the instant case, only a limited number of combinations are exemplified in the working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The solubility of B-lapachones is unpredictable, requiring each embodiment to be individually assessed. The instant claims are very broad and read on combinations of B-lapachones and any solubilizing agents, encompassing an overwhelming number of possible combinations, necessitating an exhaustive and undue search for all the embodiments suitable to practice the claimed invention. Given the sheer number of potential combinations, the diversity of potential solubilizing agents available, and the recognized unpredictability of

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this art, one would have to mount a massive additional research campaign to determine which combinations within the scope of the instant claims would exhibit the required solubility and/or reconstitution characteristics. Accordingly, applicant has failed to provide information sufficient to practice the claimed invention absent resorting to undue experimentation.

Indefiniteness Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-25 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" in claims 11 and 21 is a relative term which renders the claim indefinite. The term is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Anticipation Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4, 9, 21-23, 28, 30-38, 43, 45-49, 180, 181 and 183-187 are rejected under 35 U.S.C. 102(a), as being anticipated by Pardee et al (WO 00/61142).

The prior art discloses the use of combinations of B-lapachones and G2/M drugs such as taxol/taxotere to treat cancer. Dosages range from 0.1 mg/kg to 50 mg/kg (see the last full paragraph at page 17) and the drugs may be separated into individual vials as part of kits (page 20, first full paragraph on the page). Administration is by any of a variety of known routes, including parenteral (page 11, third paragraph). A 20mg/ml solution of B-lapachone in chemphor/ethanol is prepared in the first working example (see page 21, lines 11-13).

Regarding the requirement of certain instant claims (e.g. claims 22 and 180) that the B-lapachone be "complexed" with the solubilizing agent, it is the examiner's position that the term, interpreted as broadly as is reasonable and in light of any definitions provided by Applicant's specifications (none are present here), is inclusive of simple physical interactions which generally occur in solutions, e.g. Van Der Waal's interactions, or hydrogen bonding.

Regarding certain functional limitations of the instant claims, e.g. the requirement that a composition "remain substantially soluble" in claim 11, or that a composition "can be" freeze-dried and reconstituted in claim 21, these are merely recitations of characteristics inherent of the prior art compositions. Stated alternatively, since the prior art prepares compositions containing the same combinations of B-lapachone and

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ethanol/chremphor as Applicant, those combinations must therefore inevitably have the same physical and chemical characteristics.

Allowable Subject Matter

Claims 5, 6, 39, 40, 50, 51 and 182 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, set forth in this Office action.

Claims 14, 15, 24 and 25 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

The prior art of record does not fairly suggest, teach or disclose solubilizing a B-lapachone with a B-cyclodextrin. One could not have predicted from the prior art that using a B-cyclodextrin to solubilize a B-lapachone would have provided extremely high solubility (up to 20mg/ml) and stability, and could provide compositions which are also able to be freeze-dried, reconstituted and diluted with aqueous solution. See the instant specification at the passage spanning page 8, line 3 to page 8, line 2, and at the passage spanning page 25, lines 18 to page 26, line 8. Moreover, this meets a long-felt need in the art: see page 4, lines 28-30.

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Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick Krass whose telephone number is (703) 308-4335. The examiner can normally be reached on Monday, Tuesday and Thursday from 9am to 5pm, and on Fridays from 11am to 7pm. The examiner is off Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached at (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0193.

Frederick Krass
Primary Examiner
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